Introduction of Exogenous T-cell Receptors Into Human Hematopoietic Progenitors Results in Exclusion of Endogenous T-cell Receptor Expression.

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Public Summary:

Scientific Abstract:
Current tumor immunotherapy approaches include the genetic modification of peripheral T cells to express tumor antigen-specific T-cell receptors (TCRs). The approach, tested in melanoma, has led to some limited success of tumor regression in patients. Yet, the introduction of exogenous TCRs into mature T cells entails an underlying risk; the generation of autoreactive clones due to potential TCR mispairing, and the lack of effective negative selection, as these peripheral cells do not undergo thymic selection following introduction of the exogenous TCR. We have successfully generated MART-1-specific CD8 T cells from genetically modified human hematopoietic stem cells (hHSC) in a humanized mouse model. The advantages of this approach include a long-term source of antigen specific T cells and proper T-cell selection due to thymopoiesis following expression of the TCR. In this report, we examine the molecular processes occurring on endogenous TCR expression and demonstrate that this approach results in exclusive cell surface expression of the newly introduced TCR, and the exclusion of endogenous TCR cell surface expression. This suggests that this stem cell based approach can provide a potentially safer approach for anticancer immunotherapy due to the involvement of thymic selection.Molecular Therapy (2013); doi:10.1038/mt.2013.28.

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